TITLE : DEPRESSION OF VENTILATION BY KETAMINE IN MAN - EFFECT OF RESISTIVE LOADING

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INTRODUCTION : Ketamine is a dissociative agent which is widely used in anesthesia because of its apparent lack of depressant effect on respiration and circulation. The ventilatory response to CO_2 is reported not to be affected by ketamine in man (1). However, in this study, some patients became apneic after rapid injection of this agent. In animal studies, ketamine is responsible for a decrease in both ventilatory (2) and the occlusion pressure responses (3) during a CO_2 challenge. Airway resistance is known to be increased during general anesthesia. The use of a tracheal tube may provide an additionnal resistive load during spontaneous breathing. The present study was designed : i) to determine the effect of ketamine anesthesia on ventilation and inspiratory drive during both resting ventilation and a CO_2 stimulation test ; ii) to establish whether ketamine may exacerbate the deleterious effects on ventilation caused by the addition of a resistive load.

METHODS : Eight patients (mean age : 45.4 yrs ; mean weight : 66.2 kg) scheduled for lumbar laminectomy were included in this study, after written informed consent and institutional approval had been obtained. No patient received narcotics prior to operation. Control measurements were performed the day prior to surgery. No premedication was given. 0.5 mg i.v. atropine was given before induction. Anesthesia was induced with the infusion of 2 mg/kg ketamine over 2 minutes. A tracheal tube was inserted after i.v. succinylcholine (1 mg/kg) and a topical spray of a 5% lidocaine solution. When spontaneous respiration had been resumed, an infusion of 0.2 mg/kg/min ketamine was started. The respiratory measurements were repeated 5 minutes later. Central inspiratory activity was assessed by the measurement of minute-ventilation ($\dot{V}_E$) and occlusion pressure ($P_{0.1}$), during room-air breathing and a CO_2 stimulation test (Read's method). These measurements were repeated after the addition of a resistive load of 12.5 $cmH_2O/l/s$ in the inspiratory limb of the circuit. Linear regression equations were calculated from $\dot{V}_E$, $P_{0.1}$, mean inspiratory flow (V_T/T_I) and the duty ratio (T_I/T_{TOT}), with end-tidal PCO_2 (P_ACO_2) for each rebreathing test. Results are expressed by the slope and the position of the slope at 60 mmHg ($\dot{V}_E{}^{60}$, $P_{0.1}{}^{60}$, $V_T/T_I{}^{60}$, $T_I/T_{TOT}{}^{60}$). Student's t-test for paired data was used for statistical comparisons. All values are means ± SEM.

RESULTS : During room-air breathing : Ketamine induced no change in $\dot{V}_E$, V_T/T_I, T_I/T_{TOT} compared with control values while $P_{0.1}$ and P_ACO_2 increased markedly : from 2.0±0.1 to 2.9±0.4 cmH_2O ($p<0.05$) and from 36.1±1.5 to 42.5±1.3 mmHg ($p<0.001$) respectively.

During CO_2 stimulation : The results of $\dot{V}_E$, $P_{0.1}$ are shown in table I. There was also a drop in $V_T/T_I{}^{60}$ and a rise of $T_I/T_{TOT}{}^{60}$ under ketamine anesthesia, from control values of 1246±139 to 771±58 $ml.s^{-1}$ ($p<0.001$) and from 0.448±0.014 to 0.486±0.089 ($p<0.02$) respectively.

Effect of added inspiratory resistances : The deleterious effects of loads on $\dot{V}_E/P_ACO_2$ and $\dot{V}_E{}^{60}$ was more pronounced under ketamine anesthesia (Table I). Loaded breathing before anesthesia provoked a significant rise in $P_{0.1}$ (+ 19% ; $p<0.001$), $P_{0.1}{}^{60}$ (+ 81% $p<0.05$), T_I/T_{TOT} (+ 14% ; $p<0.001$) and $T_I/T_{TOT}{}^{60}$ (+ 28% ; $p<0.001$). This was abolished under ketamine anesthesia.

DISCUSSION : These data show that ketamine is a ventilatory-depressant agent. During both air breathing and rebreathing tests, the relationship between $\dot{V}_E$ and P_ACO_2 was depressed. This result was not due to decreased inspiratory drive since occlusion pressure remained unchanged during ketamine anesthesia. This study suggests that ketamine increases "effective" impedance of the respiratory system. The addition of a resistive load under ketamine anesthesia exacerbated the ventilation depression. The increase in inspiratory drive and duty ratio, which was induced by the addition of the load in awake subjects, was abolished under ketamine anesthesia.

	$\dot{V}_E/P_ACO_2$	$\dot{V}_E{}^{60}$	$P_{0.1}/P_ACO_2$	$P_{0.1}{}^{60}$
	l/min/mmHg	l/min	cmH_2O/mmHg	cmH_2O
C	± 1.46 / 0.30	± 33.4 / 3.9	± 0.71 / 0.29	± 7.5 / 1.2
K	± 1.07 / 0.15	± 22.4 ** / 1.7	± 0.56 / 0.13	± 8.8 / 0.8
C+R	± 1.29 / 0.37	± 29.8 / 3.9	± 0.62 / 0.13	± 12.0 / 2.7
K+R	± 0.69 *▲▲ / 0.12	± 19.8 **▲▲ / 1.5	± 0.70 / 0.09	± 9.4 / 0.9

TABLE I : Results of ventilatory and occlusion pressure responses during CO_2 stimulation. C = Control, K = Ketamine, R = added Resistance. Comparison with C (*: $p<0.05$; ** $p<0.01$). Comparison with K without added resistance (▲: $p<0.05$; ▲▲ $p<0.01$).

REFERENCES :

1. Virtue RW, Alanis JM, Mori M et al. : An anesthetic agent : 2-Orthochlorophenyl, 2-Methylamine Cyclohexanone HCl (CI-581). Anesthesiology 28 : 823-833, 1967

2. Hirshman CA, McCullough RE, Cohen PJ, Weil JV : Hypoxic ventilatory drive in dogs during thiopental, ketamine or pentobarbital anesthesia. Anesthesiology 43 : 628-634, 1975

3. Jaspar N, Mazzarelli M, Tessier C, Milic-Emili J : Effect of ketamine on control of breathing in cats. J. Appl. Physiol. 55 : 851-859, 1983